UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Dr. Bruce Alberts
President
National Academy of Sciences
2101 Constitution Avenue, NW
Washington, D.C. 20418

Dear Dr. Alberts:

I am writing to request that the National Academy of Sciences (NAS) provide recommendations to the Agency to help address the scientific and ethical questions related to whether to accept, consider, or rely on research involving deliberate exposure of human subjects to toxicants when used to identify or quantify toxic endpoints. The Agency asks that the Academy review these issues and provide recommendations that will help EPA develop appropriate factors and criteria to apply when it makes these difficult decisions. The advice of the Academy will be weighed heavily as we develop and implement a policy to govern these decisions in future.

The Agency's particular focus of concern is on studies which, since they are not conducted or supported by a federal agency, may not be performed subject to regulations that protect human subjects, such as EPA's Protection of Human Subjects Rule ("the Common Rule"), 40 CFR 26. We are particularly concerned about 'third-party' studies submitted by regulated entities for the Agency's consideration. For these purposes, EPA is considering "third-party studies" as studies that have not been conducted or funded by a federal agency pursuant to regulations that protect human subjects. These types of studies generally come to the Agency's attention only after the research has been completed and reported. At this point it is generally too late for the Common Rule requirements to apply since these requirements cover prior review and approval of proposed research, involving fully informed, voluntary consent of the participants to protect the subjects in the research.

One particular concern of the Agency is for determining the acceptability of third-party research designed to identify or quantify toxic endpoints in human subjects, such as those done to define a No Observed Adverse Effect Level (NOAEL) or No Observed Effect Level (NOEL) for systemic toxicity in humans. Studies of this kind are submitted to the agency from time to time, and have been evaluated prior to regulatory decision in several Agency programs. In the recent past most such submissions have been of studies designed to define a NOAEL for pesticide toxicity in humans.

EPA asks the Academy to undertake a critical review of appropriate standards for the scientific and ethical assessment of research entailing deliberate dosing of human subjects with toxic agents. This review should incorporate and be informed by an early open, public, participatory process through which interested people can express their suggestions or concerns to the Academy reviewers.

The Agency subscribes fully to the principles of the Common Rule and the related rules of other federal agencies, as they protect the human subjects of research conducted or supported by the federal government. We are pleased with our record of compliance with the Common Rule in our own research, and of the favorable review by our human subjects protection program in a recent survey by the National Bioethics Advisory Commission.

The Agency will consider the Academy's advice resulting from this review as we develop a policy to guide its future decisions to accept, consider, or rely on such studies in regulatory decision making. As the Academy evaluates the scientific rationale and the ethical framework for these studies, it would be most helpful if the Academy would include in its general advice responses to the following questions:

- What factors should the Agency consider in determining whether to accept, consider, or rely on human studies performed by third parties? Are there clear boundaries between acceptable and unacceptable human research? If so, what are they? If not, what range of factors should the agency consider, and how should these factors be applied in making decisions to accept, consider, or rely on specific research?

- What range of information should the Agency consider in determining whether completed research with human subjects conducted by third parties was conducted in compliance with the appropriate ethical standards, such as the Declaration of Helsinki, which may be cited in the research report?

- Do criteria such as those in the Common Rule provide an adequate framework for assessing the scientific and ethical acceptability of such studies? Should such a standard, designed to protect human participants in research, be applied after the fact to completed research conducted by third parties to determine whether it is acceptable as the basis for regulatory action?

- Are there other standards, such as the Declaration of Helsinki or various standards of good clinical practice, relevant to assessing acceptability of research to define or quantify toxic endpoints in human research subjects? Should standards intended to govern human safety studies for diagnostic or therapeutic agents be applied to research involving deliberate exposures to environmental toxins?

I look forward to meeting with you soon to work out the details and timing of your review, and to a constructive collaboration on this project.

Sincerely,

Stephen L. Johnson
Assistant Administrator

cc: E. William Colglazier
Ann Marie Mazza